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Tobacco Smoke Upper Respiratory Response Relationships in Healthy Nonsmokers[1]

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This study determined exposure–response relationships to sidestream tobacco smoke (2 hrs: 0, 1, 5, and 15 ppm CO) in 29 healthy nonsmoking young adults. Sixteen subjects had no history of environmental tobacco smoke rhinitis (ETS-NS) while 13 subjects had a history of ETS rhinitis (ETS-S). Eye irritation and odor perception showed a statistically significant exposure response in both groups; headache was significant in ETS-S and nose irritation was significant in ETS-NS subjects. Significant postexposure (P1) symptoms were first reported at 1 ppm CO among both groups, but in 3/9 symptoms were significantly greater at this exposure level in ETS-S subjects. Nasal congestion, rhinorrhea, and cough increased significantly at 15 ppm CO only. In ETS-S subjects, nasal volume decreased and nasal resistance increased in an exposure-response fashion. ETS-NS subjects had a qualitatively different shape to the exposure–response curve; significant dimensional reductions in mid- and posterior nasal volume occurred with exposure at 1 ppm CO but not at 5 ppm CO and reductions in posterior nasal volume occurred at 15 ppm CO exposure. These studies indicate subjective and objective response relationships with exposure to sidestream tobacco smoke at concentrations from 1 to 15 ppm CO. Some differences are noted among the two subject groups in the magnitude of some symptoms at the lowest exposure level and in the qualitative shape of the acoustic rhinometry and nasal resistance exposure–response curves.

Environmental tobacco smoke (ETS)[3] is one of the most common air pollutants to which people are exposed since most people spend >80% of their time indoors (Spengler and Sexton, 1992) and approximately 40% of Americans live in a home with an active smoker (National Research Council, 1986). ETS is defined as the smoke which nonsmokers inhale. It is composed of sidestream tobacco smoke (SS) (the smoke which issues from the burning end of the cigarette) and exhaled mainstream smoke (MS) (National Research Council, 1986). These two sources have demonstrable differences in content, but SS is a reasonable surrogate for controlled human studies since it contributes the largest component of ETS and can be generated consistently with a smoking machine.

Mucosal surfaces such as the bronchial passages, nasal passage, and eyes are targets of ETS, and previous investigators have reproduced mucosal symptoms with controlled human exposure to SS (Muramatsu *et al.*, 1983; Weber *et al.*, 1976). Objective evidence of acute upper respiratory responses has been lacking at exposure levels under 15 ppm CO.

Subjects with a history of "sensitive eyes" reported a higher magnitude of eye itching with exposure to 2.5 ppm CO cigarette smoke rate when compared to subjects with "not sensitive eyes" (Muramatsu *et al.*, 1983). No other studies have compared subjective and objective responses in individuals preselected for upper respiratory sensitivity or tobacco smoke-associated rhinitis.

The symptom of nasal congestion has traditionally been assessed by posterior rhinomanometry (Cole, 1989). This technique involves the placement of a tight-fitting mask on the face and having subjects hold a tube in the mouth while panting gently or performing maximal sniffs. Nasal resistance or maximum inspiratory flow is calculated. This technique has been successfully used to demonstrate decreased nasal resistance with exercise (Eccles, 1982) or vasoconstrictors and increased resistance with exposure to smoke, allergen, or histamine. The limitations of the technique are that the correlation with the symptom of nasal congestion is modest (Cole, 1982), changes in the mid and posterior regions of the nose may not be demonstrated by this technique

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[3] Abbreviations used: MS, mainstream tobacco smoke; SS, sidestream tobacco smoke; ETS, environmental tobacco smoke; ETS-S, ETS-sensitive; ETS-NS, ETS-nonsensitive; P1, postexposure.

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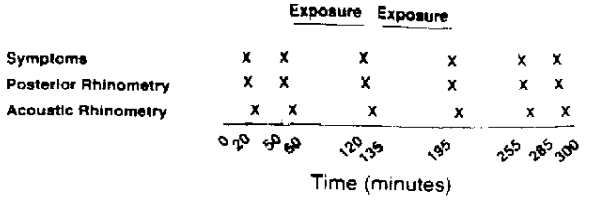

FIG. 1. Study design. The study design was a controlled challenge study with exposure on 4 days, each separated by 1 week, to clean air or sidestream tobacco smoke at a concentration of 1, 5, or 15 ppm carbon monoxide. Each subject served as his or her own control

(Bridger and Proctor, 1970), and a substantial minority of subjects are unable to be trained to perform the test. Also, it is a single test and methods to corroborate physiologic changes with dimensional changes have been lacking.

Acoustic rhinometry is a new technique that quantifies nasal cross-sectional area as a function of the distance along the nasal passage (Hilberg *et al.*, 1989). Its chief advantages for clinical and field studies are that it is rapid and noninvasive, can be measured in untrained subjects, and provides regional information about changes in the nasal passage. Initial studies have shown excellent correlations with cross-sectional area as defined by computerized tomography and water displacement techniques (Hilberg *et al.*, 1989).

The purpose of this study was to characterize upper respiratory exposure–response relationships in healthy adults to sidestream tobacco smoke at concentrations of 0, 1, 5, and 15 ppm CO. Because our previous data suggested that the presence or absence of a history of ETS-rhinitis influenced objective upper respiratory responses to smoke, exposure–response relationships were determined for two preselected groups: subjects with and without a history of rhinitis symptoms with environmental tobacco smoke exposure.

METHODS

Subject recruitment and selection. Twenty-nine healthy nonsmoking young adults, age 22–31, were recruited by advertising at a professional urban campus. Subjects had no history of chronic cardiorespiratory conditions. A questionnaire asked subjects to rate their history and severity of environmental tobacco smoke-related symptoms, as previously described (Bascom *et al.*, 1991). Sixteen reported no history of rhinitis on exposure to environmental tobacco smoke and were categorized as ETS-NS (ETS-nonsensitive), while 13 reported a history of ETS-induced rhinitis and were categorized as ETS-S (ETS-sensitive).

Subjects underwent a battery of prick skin tests to common allergens and atopy was defined as the presence of one or more positive skin tests (>1/2 the histamine diameter) (Bascom *et al.*, 1991).

Study design. The study design is shown in Fig. 1. Each subject was studied on four occasions, with each exposure separated by at least 1 week. The order of the study days was varied.

Exposure system. Subjects were studied at the University of Maryland Environmental Research Facility. Outcome measures were performed in a 41-m^3 clean room and exposures were performed in a 22-m^3 exposure room. Intake air for both rooms was filtered by HEPA filters and activated carbon filters and conditioned to constant temperature and relative humidity (71.5 ± 1°F, 42 ± 2% RH).

Sidestream tobacco smoke was generated with a 4.4-ft^3 automated smoking machine (designed by L. Sauder and built by the Department of Physiology, University of Maryland College Park). Standard 1R4F cigarettes (Tobacco and Health Institute, Lexington, KY) were preconditioned for 24 hr at 23.8°C, 60% R.H. (Tobacco and Health Institute). One, 5, or 15 cigarettes were burned simultaneously to generate SS at concentrations of 1, 5, and 15 ppm CO. Cigarettes were burned using a standard puff profile (puff duration 2 sec every minute, puff volume 35 ml achieved with 13.7 cm H_2O vacuum pressure). Cigarettes were positioned horizontally in a manifold connected to a timing device. Mainstream tobacco smoke was exhausted to the outside with a vacuum system. SS was delivered to the exposure room through a ceiling diffuser and exited the exposure room without recirculation. The ventilation rate in the exposure room was set to 120 cfm (nine air changes per hour) as recommended by ASHRAE (1989).

Monitors. Carbon monoxide concentrations as an index of cigarette smoke concentrations were monitored using two real-time carbon monoxide analyzers (Ecolyzer 2000 Series CO meter, Energetics Science, Pittsburgh, PA; Bendix Model 8501-5CA infrared gas analyzer, Lewisburg, WV). Total volatile organic compounds (HNU PI 101 trace gas analyzer, Newton, MA) were measured using isobutylene as the reference standard. Particles were enumerated with a Climet Model 226 high-resolution airborne particle analyzer/Model 8040 continuous monitor (Climet Instruments, Redlands, CA). For particle analysis, the airstream was diluted 1:224 to avoid coincidence of particles. Nicotine concentrations were determined by collecting 60-liter air samples in XAD-4 sorbent tubes (SKC, Eighty Four, PA) with an SKC universal constant-flow air sample pump computer-controlled Deluxe Model 224-PCXR7 and analyzed using gas chromatography–mass spectroscopy with a phosphorous–nitrogen detector (Maryland Spectral Services, Baltimore, MD) (Ogden *et al.*, 1989).

Symptoms. Subjects completed a questionnaire which rated the perception of odor and symptoms of eye irritation, nose irritation, nasal congestion, rhinorrhea (runny nose), chest tightness, cough, headache, and heart palpitations. Heart palpitations was chosen as a sham symptom. The scoring system was as follows: 0, symptom absent; 1, mild; 2, mild–moderate; 3, moderate; 4, moderate–severe; 5, severe. Sneezes were enumerated.

Posterior rhinomanometry system and acoustic rhinometry systems have been previously described in detail (Kesavanathan *et al.*, 1995).

Statistical analysis. The primary time point for analysis was chosen in advance as PI (immediately after the 2-hr smoke exposure); additional measures were collected to examine the time course of the response. Results were entered on spreadsheets and all data verified. Data were "doubly corrected" prior to statistical analysis, meaning that the average of two baseline measurements for the same day and the corresponding value for the clean air day were subtracted from each value. A two tailed t test was performed to determine the effect of tobacco smoke at each dose and at each time point for the ETS-S and ETS-NS groups. Analysis was performed separately for the ETS-sensitive and ETS-nonsensitive subjects and results for the two groups were compared using a two-tailed t test.

RESULTS

Subject characteristics are shown in Table 1. Differences between groups in the historical ETS-rhinitis index reflect the selection criteria. Characteristics of SS exposure conditions are shown in Table 2. Exposure conditions closely approximated target concentrations during all exposure periods.

Exposure responses for symptoms are shown in Fig. 2. Average symptoms qualitatively increased with increasing exposure in both groups for all symptoms except heart palpi-

TABLE 1
Subject Characteristics

	ETS-sensitive	ETS-nonsensitive
Sample size (N)	13	16
Age (years)	24 ± 1.6	25 ± 0.7
Gender (M/F)	3/10	7/9
Atopic (Y/N)	9/4	8/8
Number of positive skin tests	2.7 ± 0.8[c]	2.6 ± 0.8
ETS-rhinitis index[a]	5.7 ± 2.3*	0.7 ± 0.5
ETS-irritation index[a]	9.9 ± 4.1**	5.4 ± 3.9

[a] Values shown here are means ± SD. A screening questionnaire asked subjects to rate the history and severity of symptoms which had occurred with past ETS exposure. Symptoms were scored on a 0–5 scale: 0, symptom absent; 1, mild; 3, moderate; 5, severe. The ETS-rhinitis index was calculated as the sum of rhinorrhea, nasal congestion, postnasal drip, and sneezing. The ETS-irritation index was calculated as the sum of eye irritation, nose irritation, throat irritation, and headache.

* $p < 0.0001$, ETS-sensitive vs ETS-nonsensitive.

** $p < 0.01$, ETS-sensitive vs ETS-nonsensitive.

tations (chosen as a sham symptom). Eye irritation and odor perception showed a statistically significant exposure response in both groups; headache was significant in ETS-S and nose irritation was significant in ETS-NS subjects. Significant postexposure (P1) symptoms were first reported at 1 ppm CO among both groups, but 3/9 symptoms were significantly greater at this exposure level in ETS-S subjects. Nasal congestion, rhinorrhea, and cough increased significantly in both groups at 15 ppm CO only. Chest tightness increased at the 15 ppm exposure level only among subjects without a history of ETS-rhinitis. Complete time courses for mean values are shown in Tables 3A and B.. Table 4 shows a statistical comparison of the symptomatic response to controlled SS challenge in ETS-S and ETS-NS subjects at all time points. Differences in the response at the increasing concentrations of smoke were most evident with exposure to SS at a concentration of 1 ppm.

Exposure–response relationships for smoke and nasal resistance are shown in Fig. 3. Both study groups showed a significant increase in nasal resistance with exposure to SS at 15 ppm CO at P1.

Exposure–response curves for smoke and nasal dimensions measured by acoustic rhinometry are shown in Fig. 4. Subjects with a history of ETS-rhinitis showed a linear-shaped curve, with statistically significant reduction in anterior and mid-nasal volume following exposure at 15 ppm CO. No significant changes in acoustic parameters were observed at 5 ppm CO, and minimum cross-sectional area and posterior nasal volume were reduced following exposure at 15 ppm CO (Tables 5A and 5B).

DISCUSSION

ETS is a common indoor pollutant and the effects of ETS are of medical, public health, and regulatory importance. Attention has focused on long-term risk, but acute respiratory measures are also of concern. This study examined the symptomatic, physiologic and dimensional upper respiratory responses to controlled exposure to sidestream tobacco smoke at concentrations ranging from 0 to 15 ppm CO. Two groups of healthy nonsmoking subjects were studied: those with and without a history of environmental tobacco smoke rhinitis. Each subject served as his or her own control and was studied at all four concentrations; thus, individual exposure–response curves could be constructed.

Several considerations influenced the choice of exposure conditions in the present study. The ventilation rate, while currently higher than many indoor environments, was chosen

TABLE 2
Sidestream Tobacco Smoke: Measurements Made during Controlled Human Exposures

	"Clean air"[a]	1 ppm CO[b]	5 ppm CO[b]	15 ppm CO[b]
Carbon monoxide (ppm) (Bendix)	(0.4 ± 0.3)	1.2 ± 0.2	5.0 ± 0.1	14.8 ± 0.6
Carbon monoxide (ppm) (Ecolyzer)	(1.4 ± 0.3)	1.4 ± 0.3	5.3 ± 0.4	14.6 ± 1.1
Organic vapors (ppm) (HNU)	(0.9 ± 0.2)	0.4 ± 0.2	0.4 ± 0.2	1.3 ± 0.5
Nicotine ($\mu g/m^3$)	(<1.67) (lower limit of detection)	73 ± 5	305 ± 16	958 ± 33
Particles (μm) (Climet)				
0.3–0.5	$(3.2 \pm 0.4 \times 10^4)$	$1.1 \pm 0.0 \times 10^7$	$5.0 \pm 0.8 \times 10^7$	$2.0 \pm 0.2 \times 10^8$
0.5–0.7	$(9.8 \pm 2.5 \times 10^3)$	$2.0 \pm 0.6 \times 10^6$	$1.2 \pm 0.2 \times 10^7$	$6.3 \pm 1.0 \times 10^7$
0.7–1	$(2.6 \pm 1.2 \times 10^3)$	$2.6 \pm 0.1 \times 10^5$	$1.8 \pm 0.3 \times 10^6$	$1.2 \pm 0.3 \times 10^7$
1–3	$(1.2 \pm 0.5 \times 10^3)$	$4.1 \pm 0.3 \times 10^4$	$2.4 \pm 0.4 \times 10^5$	$1.7 \pm 0.4 \times 10^6$
>3	$(2.4 \pm 1.1 \times 10^2)$	$5.1 \pm 0.6 \times 10^2$	$3.1 \pm 0.9 \times 10^2$	$1.5 \pm 0.4 \times 10^3$

Note. All values are means ± SEM.

[a] Values for 0 ppm CO represent background levels.

[b] Values for 1, 5, and 15 ppm CO represent net increases over background levels.

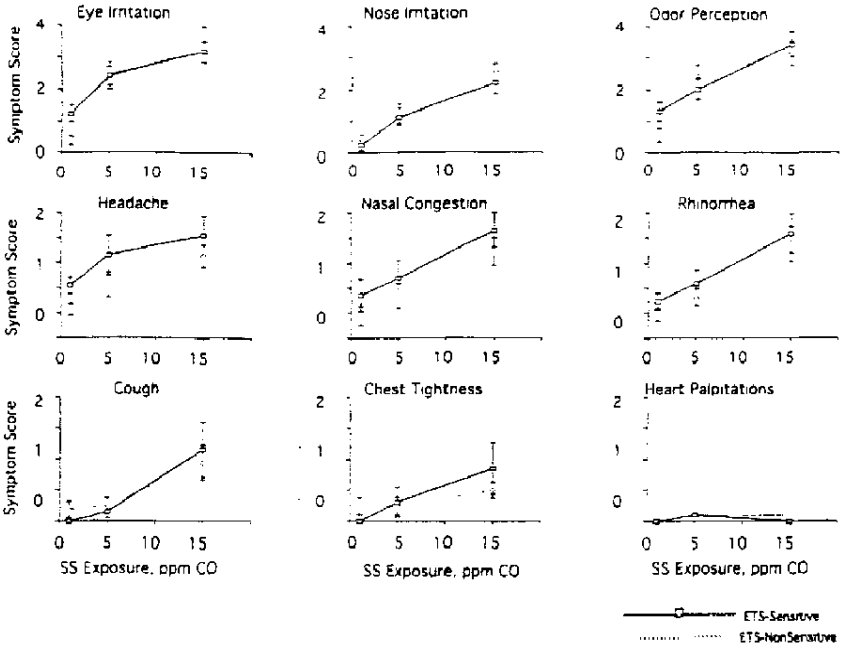

FIG. 2. Symptomatic response to challenge with clean air or sidestream tobacco smoke at concentrations of 1, 5, and 15 ppm CO. Shown are the symptoms reported at the completion of the 2-hr exposure period (P1). Values are the means ± SEM of symptoms rated on a 0–5 scale for the 13 ETS-sensitive subjects (squares and solid lines) and the 16 ETS-nonsensitive subjects (diamonds and dashed lines). Values are corrected for the preexposure baseline and the comparable value on the 0 ppm CO exposure day. Tables 3A and 3B show complete time courses and results of statistical tests.

based on the American Society for Heating, Refrigeration and Air Conditioning Engineers (ASHRAE) recommendations for smoking rooms (1989). The air was "single pass," meaning it was not recirculated, to foster uniformity of conditions. The 1 ppm exposure level was maintained by burning one cigarette at a time throughout the exposure period.

TABLE 3A
Symptomatic Response to SS in ETS-Sensitive Subjects

	Exposure condition											
	1 ppm CO				5 ppm CO				15 ppm CO			
Symptom	Mid-Exp	Post1	Post2	Post3	Mid-Exp	Post1	Post2	Post3	Mid-Exp	Post1	Post2	Post3
Headache	0.2	0.5[c]	0.2	0.2	0.5[a]	1.2[d]	0.5	0.4	1.1[d]	1.5[e]	1.2[e]	0.8[a]
Eye irritation	0.9[e]	1.2[d]	0.4	0.2	1.8[e]	2.4[e]	0.7[a]	0.3	3.3[e]	3.2[e]	1.0[e]	0.4[c]
Nose irritation	0.5[a]	0.2	0.1	0.3	1.0[e]	1.1[e]	0.3	0.2	2.2[e]	2.2[e]	0.5[d]	0.3
Nasal congestion	0.4	0.3	0.1	0	0.2	0.7	0.2	0	1.3[d]	1.7[d]	0.7[a]	0.3
Rhinorrhea (runny nose)	0.4[a]	0.2	0.2	0.1	0.3	0.6	0	0	1.3[b]	1.6[e]	0.2	0.1
Sneezes	0	0	0	0	0.1	0.2	0.2	0	0.2	0.4	0.2	0
Odor perception	1.2[e]	1.3[d]	0.3	0.2	2.2[e]	2.0[e]	0.5	0.3	3.5[e]	3.5[e]	0.9[d]	0.6[b]
Chest tightness	0	0	0	0	0.1	0.3	0.2	0.1	0.8	0.8	0.2	0
Cough	0.1	0	0	0	0	0.2	0	0	1.0[d]	1.2[d]	0	0
Heart palpitations	0	0	0	0	0	0.1	0	0	0.1	0	0	0

Note. Values shown are mean values ($n = 13$) for doubly corrected data. Raw values are corrected by subtracting the average of two preexposure baseline measurements for the same study day and the value for the comparable time point on the clean air day. Statistical analysis was Student's t test (two tailed). Significance is shown as follows: [a] $p < 0.05$, [b] $p < 0.01$, [c] $p < 0.005$, [d] $p < 0.001$, [e] $p < 0.0001$.

TABLE 3B
Symptomatic Response to SS in ETS-Nonsensitive Subjects

	Exposure condition											
	1 ppm CO				5 ppm CO				15 ppm CO			
Symptom	Mid-Exp	Post1	Post2	Post3	Mid-Exp	Post1	Post2	Post3	Mid-Exp	Post1	Post2	Post3
Headache	−0.1	0.1	0.1	0.1	0.3	0.6[a]	0.2	0.3[a]	0.6[a]	1.1[c]	0.4[a]	0.3
Eye irritation	0.6[b]	0.4[a]	0.2	0.1	2.2[c]	2.4[c]	0.3[a]	0.2[a]	3.7[c]	3.8[c]	0.9[d]	0.4[a]
Nose irritation	0.2	0.4[a]	−0.1	−0.1	1.3[c]	1.2[d]	0.3[a]	0.2	2.3[c]	2.5[c]	0.3[a]	0.2
Nasal congestion	−0.2	−0.1	−0.3	0.1	−0.1	0.3	−0.2	−0.1	0.9[c]	1.2[d]	0.1	0.2
Rhinorrhea (runny nose)	0	0	0.2	−0.1	−0.1	0.3	0.2	0	1.5[c]	1.4[c]	0.3	0.2
Sneezes	−0.1	−0.1	−0.1	−0.1	0	0.1	0.1	0.1	0.3	0.3	−0.1	−0.1
Odor perception	0.7[a]	0.6[a]	0.2	0.1	2.1[c]	2.4[c]	0.7[a]	0.6[a]	3.4[c]	3.2[c]	0.9[c]	0.6[a]
Chest tightness	0	0	0	0	0.3	0.3	0.1	0.1	0.6[c]	0.5[c]	0.1	0
Cough	0.1	0.2	0.2	0.1	0.3	0.3	0.1	0.1	1.0[d]	0.9[c]	0.1	0.1
Heart palpitations	0	0	0	0	0.1	0.1	0	0	0.2	0.1	0	0

Note. Values shown are mean values (n = 16) for doubly corrected data. Raw values are corrected by subtracting the average of two preexposure baseline measurements for the same study day and the value for the comparable time point on the clean air day. Statistical analysis was Student's t test (two tailed). Significance is shown as follows: [a] $p < 0.05$, [b] $p < 0.01$, [c] $p < 0.005$, [d] $p < 0.001$, [e] $p < 0.0001$.

The exposure room is similar in size to a small conference room, and adequate mixing of the smoke occurred with the use of the central ceiling diffuser, in-room fans, and an exit duct at the base of the wall in each corner.

Previous investigators have used an irritation index for the symptom score that included both the perception of irritation and possible end-organ responses (e.g., nose flow, itching, dryness, and blocked-up nose) (Weber *et al.*, 1976). In our study we distinguish between the perception of irritation and the rhinitis response. This is because to two events are mediated through different pathways (Dias *et al.*, 1995). The perception of irritation occurs via the trigeminal nerve with influence from the olfactory nerve and cognitive interpretation of the perceptions. The rhinitis response includes efferent pathways such as parasympathetic glandular stimulation, mediator-induced vascular leakage, and vasodilation (Raphael *et al.*, 1991). In this study, subjects preselected for smoke-induced rhinitis also reported a greater history of smoke-associated irritation (Table 1).

Acute upper respiratory symptoms caused by SS exposure have been demonstrated with previous controlled human exposure studies. Investigators (Weber *et al.*, 1976) performed

TABLE 4
Comparison of the Symptomatic Response to Sidestream Tobacco Smoke in ETS-Sensitive and ETS-Nonsensitive Subjects

	Exposure condition											
	1 ppm CO				5 ppm CO				15 ppm CO			
Symptom	Mid-Exp	Post1	Post2	Post3	Mid-Exp	Post1	Post2	Post3	Mid-Exp	Post1	Post2	Post3
Headache	0.01	0.03	ns	ns	ns	ns	ns	ns	ns	ns	0.02	ns
Eye irritation	ns	0.006	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Nose irritation	ns	ns	ns	0.05	ns	ns	ns	ns	ns	ns	ns	ns
Nasal congestion	0.09	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Rhinorrhea (runny nose)	0.04	ns	ns	ns	0.03	ns	ns	ns	ns	ns	ns	ns
Sneezes	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Odor perception	0.04	0.05	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Chest tightness	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Cough	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Heart palpitations	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns

Note. Values shown are the significance probabilities which are less than 0.1 (ns represents a probability value greater than 0.1). The mean for ETS-sensitive subjects (n = 13) was compared to the mean for ETS-nonsensitive subjects (n = 16) using Student's t test (two-tailed).

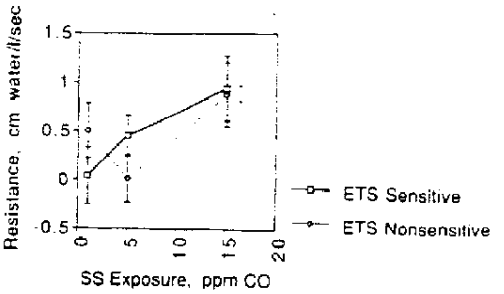

FIG. 3. Effect of controlled challenge with sidestream tobacco smoke on nasal resistance, determined by posterior rhinomanometry. Shown are the values measured at the completion of the 2-hr exposure period (P1). Values are the means ± SEM of nasal resistance for the 13 ETS-sensitive subjects (squares and solid lines) and the 16 ETS-nonsensitive subjects (diamonds and dashed lines). Values are corrected for the preexposure baseline and the comparable value on the 0 ppm CO exposure day. *$p \leq 0.05$ P1 (15 ppm CO) vs P1 (0 ppm CO).

26-min challenges with sidestream tobacco smoke at concentrations that rose during the interval from 1 to 71 ppm CO. Subsequent studies (Muramatsu *et al.*, 1983) performed challenges at smoke concentrations rising to 1.3 and 2.5 ppm CO for 1 hr. Our study used smoke concentrations that were consistent over the 2-hr exposure period and included 0, 1, 5, and 15 ppm CO exposure levels. In all three studies, eye symptoms were reported to be of the greatest magnitude, with nasal symptoms present at a lower level. This suggests that the differences in symptom magnitude between organs caused by smoke exist over a wide range of exposure conditions.

Subjects were not informed of the study conditions. To assess the possibility that study subjects were reporting implausible symptoms, the symptom heart palpitations was included as a sham symptom. This symptom showed no exposure–response relationship, suggesting that there was not a general pattern of overreporting at either baseline or related to a perception of increasing smoke concentration.

Increases were noted in symptoms indicative of effects on the eye, nose, and chest. Headache, which also increased with smoke exposure, is often regarded as a central nervous system symptom, but may occur with nasal disease (e.g., sinusitis). Odor perception increased with increasing smoke concentration, indicating that a plateau in the exposure–response relationship or "odor fatigue" was not occurring under these exposure conditions.

To determine objective measures of upper respiratory response to tobacco smoke, we used the distinct but complementary methods of posterior rhinomanometry and acoustic rhinometry. Posterior rhinomanometry is a well-established physiologic measure of upper respiratory function (Cole, 1989) but does not allow localization of effects within the nasal passage. The present study shows evidence of increased nasal resistance with smoke exposure at 15 ppm CO, confirming earlier studies. Acoustic rhinometry is a new test with which local dimensional changes can be measured by integrating the nasal passage cross-sectional area over a spatial interval. New information obtained in this study is that widespread reductions in nasal dimensions occur with 15 ppm CO smoke exposure in both study groups.

A second aim was to compare the response to controlled SS challenge in subjects with a variable history of ETS-rhinitis. Variable symptoms with exposure to tobacco smoke have long been recognized clinically (Speer, 1968). Patients may say that they are "allergic to tobacco smoke" but studies do not support an IgE-mediated etiology for tobacco smoke-associated rhinitis (Bascom *et al.*, 1991). While IgE-mediated mechanisms are relatively well understood, no similar understanding exists of the basis for increased responsiveness to irritants in humans. Differential sensitivity to irritants is thus well recognized but poorly understood (Bascom, 1992).

Previous studies have suggested that there might be differences in the response to environmental tobacco smoke for healthy subjects with or without a history of smoke-induced rhinitis. Challenge with brief, high levels of tobacco smoke (45 ppm CO, 15 min) in subjects with and without a history

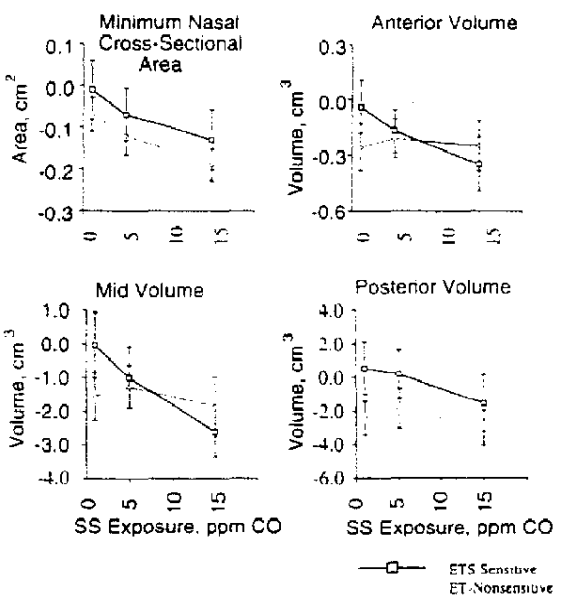

FIG. 4. Effect of controlled challenge with sidestream tobacco smoke on nasal dimensions as determined by acoustic rhinometry. Shown are the values measured at the completion of the 2-hr exposure period (P1). Values are the means ± SEM of nasal cross-sectional area and nassal volume for 13 ETS-sensitive subjects (squares and solid lines) and the 16 ETS-nonsensitive subjects (diamonds and dashed lines). Values are corrected for the preexposure baseline and the comparable value on the 0 ppm CO exposure day.

TABLE 5A
Acoustic Rhinometry and Posterior Rhinomanometry Response to SS in ETS-Sensitive Subjects

	Exposure condition											
	1 ppm CO				5 ppm CO				15 ppm CO			
	Mid-Exp	Post1	Post2	Post3	Mid-Exp	Post1	Post2	Post3	Mid-Exp	Post1	Post2	Post3
Bilateral amin	−0.07	−0.01	−0.09	−0.03	−0.05	−0.07	−0.13	−0.01	−0.19[a]	−0.13	−0.12	−0.03
Bilateral V1	−0.18	−0.04	−0.10	−0.07	−0.22	−0.17	−0.25	−0.03	−0.54[b]	−0.35[c]	−0.29[a]	−0.13
Bilateral V2	−1.0	−0.04	−0.49	−0.12	−1.06	−1.0	−1.41	−0.64	−2.96[b]	−2.61[c]	−1.55	−1.20
Bilateral V3	−2.35	0.55	0.21	1.31	−0.80	0.16	−1.1	4.0	−2.96	−1.55	−0.62	0.08
Bilateral nasal airway resistance	0.2	0.4	0.1	0.2	0.1	0.4	0.4	0.3	1.2[a]	0.9[c]	0.8	0.0

Note. Values shown are mean values (n = 13) for doubly corrected data. Raw values are corrected by subtracting the average of two preexposure baseline measurements for the same study day and the value for the comparable time point on the clean air day. Statistical analysis was Student's t test (two-tailed). Significance is shown as follows: [a] $p \leq 0.05$, [b] $p \leq 0.01$, [c] $p \leq 0.005$.

of ETS-rhinitis (Bascom *et al.*, 1991) showed headache, nasal congestion, chest tightness, and cough among subjects with a history of ETS-rhinitis only. The present study shows that the magnitude of the symptoms of eye irritation, headache, and odor perception were greater postexposure to 1 ppm smoke among subjects with a history of ETS-rhinitis. Rhinorrhea was greater and nasal congestion tended to be greater among the same group after 1 hr exposure at 1 ppm CO. The present study does not define the full exposure–response curve, so it is not possible to determine an ED50 for each group. Inspection of the curves suggests a parallel shift of the exposure response curves for symptoms of headache, nasal congestion, and rhinorrhea.

Our study found differences in the concentration × time response between the ETS-sensitive and ETS-nonsensitive groups. ETS-sensitive subjects reported increasing levels of eye irritation from 1 hr (Mid-Exp) to 2 hr exposure (P1), e.g., 0.9 to 1.2 at 1 ppm CO and 1.8 to 2.4 ppm at 5 ppm CO. In contrast, ETS-nonsensitive subjects reported no change in the magnitude of eye irritation at these time points (e.g., 0.6 to 0.4 at 1 ppm CO and 2.2 to 2.4 at 5 ppm CO). Muramatsu *et al.* reported that subjects with a history of "sensitive eyes" reported a more rapid rise and a higher maximum symptom of "eye itching" with a 1-hr exposure to smoke at a concentration of 2.5 ppm CO (1983).

Previous data also suggested that there might be differences in the objective upper respiratory exposure–response relationships to environmental tobacco smoke. Subjects with a history of ETS-rhinitis show an increased nasal resistance with brief high-level exposure (45 ppm CO, 15 min), while subjects without a history of ETS-rhinitis do not (Bascom *et al.*, 1991). At moderate, prolonged exposures (15 ppm, 1 and 2 hr), changes in nasal resistance are similar in the two groups.

Nasal congestion resulting from smoke exposure is thought to be due to vascular congestion. The evidence for this is that α-adrenergic vasoconstrictors partially block the congestive response to smoke (Bascom and Fitzgerald, 1994)

TABLE 5B
Acoustic Rhinometry and Posterior Rhinomanometry Response to SS in ETS-Nonsensitive Subjects

	Exposure condition											
	1 ppm CO				5 ppm CO				15 ppm CO			
	Mid-Exp	Post1	Post2	Post3	Mid-Exp	Post1	Post2	Post3	Mid-Exp	Post1	Post2	Post3
Bilateral amin	−0.07	−0.07	−0.05	−0.04	−0.1[a]	−0.12	−0.04	−0.04	−0.13[c]	−0.19[a]	−0.02	−0.07
Bilateral V1	−0.12	−0.26	−0.19	−0.31	−0.21[a]	−0.21	0.05	−0.19	−0.27[c]	−0.25	−0.04	−0.22
Bilateral V2	−1.14	−1.57[a]	−1.22	−1.71	−1.12	−1.28	−0.38	−1.09	−0.20[c]	−1.87	−1.07	−1.51
Bilateral V3	−1.45	−2.41[a]	−2	−1.73	−0.82	−1.85	−1.13	−0.58	−2.04[a]	−3.03[c]	−2.5	−1.08
Bilateral nasal airway resistance	−0.4	0.5	0.7	0.6[a]	0.5	0	0.4	0.6	1.2	0.9[a]	0.4	0.8[a]

Note. Values shown are mean values (n = 16) for doubly corrected data. Raw values are corrected by subtracting the average of two preexposure baseline measurements for the same study day and the value for the comparable time point on the clean air day. Statistical analysis was Student's t test (two-tailed). Significance is shown as follows: [a] $p \leq 0.05$, [b] $p \leq 0.01$, [c] $p \leq 0.005$.

and that previous nasal lavage results at a brief, high level and prolonged moderate levels of exposure show no evidence of vascular leak or glandular stimulation (Bascom *et al.*, 1991; Willes *et al.*, 1991).

In this study, a surprising result was observed. Reduced nasal volume occurred with low-level smoke exposure (1 ppm CO) in the subjects with no history of ETS-rhinitis, but did not occur in subjects with a history of ETS-rhinitis. This finding achieved statistical significance using acoustic rhinometry, a technique that has been shown to have better sensitivity than posterior rhinomanometry (J. Kesavanathan, unpublished data).

In summary, this study examines the symptomatic, physiologic, and dimensional response to smoke exposure at concentrations of 0, 1, 5, and 15 ppm CO. These studies indicate subjective and objective response relationships with exposure to sidestream tobacco smoke at concentrations from 1 to 15 ppm CO. Some differences are noted among the two subject groups: the subjects with a history of ETS-rhinitis report significantly greater headache, eye irritation, odor perception, and rhinorrhea at the 1 ppm exposure level but not at higher exposure levels. The subjects with no history of ETS-rhinitis showed significant reductions in nasal volume with exposure to 1 ppm CO and a trend toward a complementary increase in nasal resistance. Both groups of subjects demonstrated similar levels of congestion and symptoms with exposure to 15 ppm CO.

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